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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
SHUKLA, R	
ART UNIT	**PAPER NUMBER**
1632	13

DATE MAILED: 12/18/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/340,283	MESSING ET AL.	
	Examiner	Art Unit	
	Ram Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *1-9,11-28 and 40-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10 and 29-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

1. Amendment filed 10-4-2000 (paper # 9) has been entered.

2. New claims 29-53 have been entered.

Election/Restrictions

3. Claims 1-9 and 11-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 6.

4. Newly submitted claims 40-53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Newly presented claims are drawn to a method of identifying compounds that modulate consumption of a drug of abuse, because as noted in the original restriction requirement (office action of 12-16-99), the parameters of determining effects of a chemical on drug abuse (drug dependence) and that of determining effects on anxiety are not the same. Furthermore, the subjects used in a method of screening for compounds that modulate anxiety will also be different from the subjects used in the method of screening for a compound that modulates drug dependence. Therefore, the method of newly presented claims would have different steps and subjects than those required in the originally elected claims.

Election was made **without** traverse in Paper No. 6.

5. Claims 10 and 29-39 are instantly under consideration.

Oath/Declaration

6. The oath/declaration has been entered.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 10 and 29-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling for a claimed invention, one considers whether the specification itself or prior art discloses sufficient guidance and ample exemplification and whether there is sufficient evidence that an artisan of skill would have been able to make and use the invention as claimed without undue experimentation. In the instant case, the invention recites a method of identifying compounds that modulate anxiety, said method may have only one step comprising testing effect of the compounds on the activity of PKC-epsilon which would indicate that the compound has anxiety modulating effects or said method comprises a step of first determining whether a compound modulates PKC-epsilon activity and then testing its anxiety modulatory activity in a subject. In different claims the invention encompasses in vivo and in vitro methods of monitoring the activity of PCK-epsilon and determination of the anxiety modulation in a subject. The specification is not enabling for the claimed method because the specification has not disclosed sufficient guidance to make and practice the claimed method in a subject and an artisan of skill would have required undue experimentation to practice the claimed method.

First issues is, what is the method of testing the PKC-epsilon modulatory activities of a compound, would it be determined in in vitro system or in in vivo system? Specification on page 29-32 (starting on lines 25-30 on page 29 continued till page 36) discloses assays used for identifying compounds that modify the activity of PKC-epsilon and that such compounds may be inhibitors or activators of PKC-epsilon activity and that cells expressing PKC-epsilon or purified enzyme preparations or enzyme immobilized on solid support may be used for screening such compounds. While the methods of assaying the modulation of PKC-epsilon's activity by compounds is well known in the art, the question is: can the results obtained in in vitro systems be extrapolated to in vivo systems or can an effect on the activity of PKC-epsilon in vitro be reproduced in vivo when the same compound is given to an animal in vivo? It is noted that similar in vivo and in vitro effects of a compound on PKC-epsilon activity is crucial to practicing the claimed invention. It is well known in the prior art that effects of compounds on a purified

preparation of an enzyme may not be necessarily reproduced when the same assay is carried out in a cell culture system. Likewise, the effects of a compound in a cell culture system may not be reproducible when the same compound is administered to an animal because the milieu of growth factors that regulate the growth and differentiation of an cell in vitro in cell culture may be very different that those in vivo. Therefore, it is not clear how can effects of a compound on the activity of PKC-epsilon be considered as an indicator of its anxiety modulatory activity. Specification on page 26 summarizes the characteristics of a transgenic mouse wherein both the alleles of PKC-epsilon gene have been inactivated. The specification asserts that while this mouse has a normal body weight, eating, drinking and normal gross locomotor behavior, it demonstrated differences when open-field activity, exploration of a novel object, and elevated plus maze performances were tested. Some of the studies that characterized the PKC-epsilon null mouse are described in figures 1-21. It is noted that figures 5 and 7-9 disclose data from both male and female mice and there are clear differences in the data related to the two sexes of mice. For example, as disclosed in figure 5, there was no difference in body weight of mutant male or female mice, when the body weight was compared with the same sex control, however, when body weight of male and female mice was compared there was significant difference between both wild type and mutant mice. It is not clear what is meant by these observations because a significant weight difference between wild type male and female mice will negate the change in the weight of mutant male Vs female mice. Likewise, figure 9 compares the performance of wild type and mutant male and female mice in elevated pus maze test. In this test, while the male mutant mice compared to male wild type mice showed higher scores, however, the differences between wild type and female mutant mice were not significant, if any thing they were reverse of male, i.e. wild type had higher values compared to mutant. Rest of the figures do not indicate whether the tests or studies were done in male or female mice. If one anticipates that these studies would have been done in male mice because effect of mutation was more consistent, then one can also infer that mutant female mice of the invention can not be reliably used in the recited method. Next, can the activity of a compound be tested for PKC-epsilon modulation in the mutant mouse disclosed in the application? Since the mouse is not expressing this isoform of PKC and there are differences between the male and female mice in terms of the symptoms of anxiety tested, the role of PKC-epsilon in anxiety is not clear, particularly in view of the difference in the results related to male an female mice. Therefore, it is not clear whether there is a clear correlation between anxiety and PKC-epsilon and therefore

there is no evidence that a compound that alters the activity of PKC-epsilon activity will modulate. In summary, the specification does not provide convincing evidence that change in PCK-epsilon activity due to exposure or treatment with a compound shows that the compound has anxiety modulatory activity. Additionally, the specification does not provide sufficient disclosure and direction as to how an artisan have determined in vivo that a compound had anxiety modulatory activity and an artisan would have required undue experimentation to determine whether a compound that modulated PKC-epsilon activity in vitro would have also modulated PKC-epsilon activity in vivo.

Next question is: what is a subject, who can be used for determining efficacy of a compound in modulating the state of anxiety? The specification as filed does not explicitly define what a subject will be? However, conventionally it is interpreted as a test animal. Then the question is can any animal be a subject for determining efficacy of a compound in modulating the activity of anxiety. The specification as filed is not enabling for using any animal as a subject in practicing the claimed method because an artisan of skill would not know what characteristics an animal should have to be considered as a subject for anxiety modulatory compound testing. In claim 31, the method indicates that the symptoms of anxiety can be decreased locomotor activity, decreased time in open areas, decreased exploratory behavior, and increased basal level of a stress hormone. However, the specification does not disclose that a subject should have these characteristics to qualify as a subject. Furthermore, what if only one characteristic is present in a subject or an animal, can that be used in the method. It is not clear from the disclosure as to if any of the symptoms listed above were present in an animal, the animal would still be an appropriate subject for the method.Additionally, there is nothing in the specification as to how an artisan would have determined or whether an artisan would have determined whether a change in the above listed behaviors is only because of anxiety, not because of some other reasons. The only animal model or subject discussed in the specification is a PKC-epsilon mutant mouse (-/-) and a wild type mouse. As stated earlier while the male transgenic mice that are PKC-epsilon null mutant shows reduced anxiety related behavbior, open-field activity, exploration of a novel object, and elevated plus maze performances, it can not be used as a subject in the claimed method because it does not have the PKC-epsilon enzyme. It is not clear from the disclosure in the specification whether female mutant mice (null for PKC-epsilon) have reduced anxiety-related characteristics. The results

discussed in the specification are on a wild type mouse compared to those in a mutant mouse, however, the mutant mouse is not an anxiety model while a wild type mouse would not have anxiety characteristics, therefore, It is not clear how results obtained in these animals can be indicative of anxiety animal model. Therefore, the specification is not enabling for the use of an animal in the claimed method since the specification does not disclose what characteristics should be present in an animal for it be a subject in the claimed method.

Rogers et al (Rogers DC. Behavioral Brain Research 105: 207-217, 1999) teach that there are marked differences in the behavior phenotype of six inbred strains of mice, which would indicate that any mice may not be used for comparing phenotypes of mice (see abstract), therefore, change in the behavior in an animal, such as those recited may not even be due to anxiety, rather they may be essentially due to natural variation. The specification does not disclose as to how there characteristics as recited can be used in the claimed method to reliably determine that a compound has anxiety modulatory effects.

Next, the specification in example 7, page 61, lines 21-31 continued on page 62, lines 1-11, disclose the results of an experiments in which effects of PKC-epsilon inhibitor on PKC-epsilon activity was determined in vitro using microsac preparations from PKC-epsilon mutant mice treated with GABA receptor modulator. While this experiment showed the involvement of PKC-epsilon activity in GABA receptor mediated chloride transport, it does not indicate that PKC-epsilon inhibitor would have modulated anxiety symptoms as claimed. The invention of claim 29 would encompass that the inhibition of PKC-epsilon activity by a compound is not specific, which would indicate that the compound might inhibit any other activity in the subject or animal. This is in confirmation with the issue raised above that the effects of a compound in vivo and in vitro would not be same and therefore, specificity may not be there. Accordingly, a compound that inhibits only PKC-epsilon in a purified preparation may inhibit other enzymes or other isoforms of PKC. For example, an inhibitor of PKC that inhibits the activity of calcium independent PKC isoforms would inhibit not only PKC-epsilon but also PKC-delta since both these PKC isoforms are calcium independent (Berg et al. Molecular Pharmacology 45:826-836, 1994). Additionally, it is not clear as to whether general inhibitors of PKC may also have anxiety modulatory effects, for example, those disclosed in US Patent 5,270,310. However, the specification does not provide any guidance whether any and all PKC-epsilon inhibitors would have anxiety modulatory effects. Furthermore, claim 34 recites that the PKC-epsilon is at least partially purified, however, it is not clear whether a partially purified PKC-epsilon is

contaminated with other PKC isoforms or other kinases. For example, if the PKC-epsilon preparation (partially pure) contains other PKC isoforms, it is not clear, how would inhibition of such an impure enzyme preparation by a compound can be relied upon for anxiety modulatory activity since the inhibition observed may not be due to effect on PKC-epsilon, rather it can be due to inhibition of other kinases or other isoforms of PKC. For example, a broad kinase inhibitor may inhibit all the kinases, however, such an effect would not be specific for PKC-epsilon or even PKC. Therefore, the specification does not provide sufficient guidance whether an inhibitor of PKC-epsilon would have anxiety modulatory activity and an artisan would require undue experimentation to practice the method as claimed.

In conclusion, the specification is not enabling for the claimed method because the specification fails to provide sufficient evidence whether a compound that affects PKC-epsilon would have anxiety modulatory activity and the specification fails to provide sufficient guidance as to what would have been considered a subject or an animal model of anxiety and an artisan of skill would have required undue experimentation to make and use the claimed invention.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

10. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 recites the limitation "the symptoms of anxiety" in line 3, however, no symptoms of anxiety are disclosed. There is insufficient antecedent basis for this limitation in the claim.

Claims 29 and 30 recites the limitation "said symptoms of anxiety" in line 2, however, no symptoms of anxiety are disclosed in this claim or in claim 10 . There is insufficient antecedent basis for this limitation in the claim.

Claim 35 is vague and indefinite because it recites "the animal's symptoms of anxiety," however, the claim does not recite any animal with symptoms of anxiety.

Claim 31 is vague and indefinite because it is unclear as to what is meant by the term "stress hormone."

11. Applicant's arguments with respect to claim 10 have been considered but are moot in view of the new ground(s) of rejection.

12. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

Scott D. Priebe

Ram R. Shukla, Ph.D.

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER